## *Remarks*

Upon entry of the foregoing amendment, claims 55-84, 106-111, 113, 114 and 130-148 are pending in the application, with claim 55. 56, 71, 72, 106, 113 and 136 being the independent claims. Claims 72-84, 106-111, 136, 137 and 141 are withdrawn. Claims 55, 56, 71, 113 and 133 are sought to be amended. Support for the amendments to claims 55, 56, 71 and 113 may be found, e.g., in Figure 19 and throughout the specification as filed. Support for claim 133 may be found in the parent claims 55, 56, 71 and 113. No new matter has been added by these amendments.

Based on the amendments and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding rejections and that they be withdrawn.

***Objections to the Claims***

The Examiner objected to claim 133 under 37 C.F.R. § 1.75(c), as allegedly being of improper dependent form for failing to limit the subject matter of a previous claim. Applicant respectfully traverses this rejection.

Solely to advance prosecution, and not in acquiescence to the Examiner's objection, Applicant has amended the claim to recite the language "self-complementary" as recited in parent claims 55, 56, 71, and 113.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the objection.

***Rejection under 35 U.S.C. § 103***

***The First 103 Rejection***

The Examiner rejected claims 55-70, 113, 130, 133-135, 138-140, 142-148 under 35 U.S.C. § 103(a) as allegedly unpatentable over Dattagupta (U.S. Pat. No. 5,215,899) in view of Sasaki *et al.* The Examiner contends that Dattagupta discloses, *inter alia*, hybridization of an abortive promoter cassette with a single stranded target polynucleotide and that while Dattagupta does not disclose the incorporation of a terminator in the reaction, such would be obvious in view of the teachings of Sasaki *et al.* The Examiner contends that Sasaki *et al.* discloses a transcriptional sequencing method comprising, *inter alia*, hybridizing a single stranded target polynucleotide with an abortive promoter cassette comprising a sequence that hybridizes to the single stranded target polynucleotide, and a region that can be detected by transcription by a polymerase. The Examiner contends that Sasaki *et al.* discloses incubating the target polynucleotide with an RNA polymerase, an initiator, and a terminator and detecting the oligonucleotide transcripts by electrophoresis sequencing method.

The Examiner contends that while Sasaki *et al.* involve a different method for transcriptional sequencing, one of ordinary skill in the art would have clearly recognized that the method provided for by Dattagupta would also have been capable of conducting transcriptional sequencing by incorporating nucleotide chain terminators in their reaction. The Examiner further contends that one of ordinary skill in the art would have had a reasonable expectation of success at combining the teachings since both methods involve generation of nucleic acid constructs comprising promoter sequences. Applicant respectfully traverses this rejection.

Applicant respectfully disagrees with the Examiner's analysis of the cited art. Applicant's claims are not directed to transcriptional sequencing methods as discussed by Sasaki *et al.* Applicant's claims are directed to methods of detecting DNA or RNA in test samples. Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicant has amended the claims to more particularly point out and distinguish that the transcription reaction proceeds by an abortive, reiterative process. This language makes clear that the claims do not encompass embodiments wherein a plurality of transcripts of very different sizes are generated, as would be the case in transcriptional sequencing methods. The claims recite that the transcripts are generated by an abortive, reiterative process. An abortive, reiterative process is shown in Figure 19 of the specification. Figure 19 shows how trinucleotide or tetranucleotide products are generated with RNA polymerase, labeled GpA or GpApA initiator, and a labeled pppG or pppA terminator on an abortive promoter cassette molecule. The reaction is reiterative because the same oligonucleotide product is generated repetitively, one after the other, on the same template. Applicant's claims are directed to abortive, reiterative methods and do not encompass the transcriptional sequencing methods of Sasaki *et al.*, which generate a plurality of transcripts of very different sizes. Such an interpretation of an abortive, reiterative process would clearly run afoul to the way these terms would be understood by a person of ordinary skill in the art in view of Applicant's specification.

Accordingly, the Examiner's rationale for incorporating chain terminators in the method of Dattagupta is not relevant, because the claims clearly specify that transcription occurs by a reiterative, abortive process. This process described by Sasaki *et al.* is not

reiterative and abortive because a plurality of transcripts of very different sizes are generated.

Notwithstanding the Applicant's amendment to the claims to recite that the reaction is reiterative and abortive, Applicant disagrees with the Examiner's analysis of the cited art and the rejection. First, Applicant respectfully disagrees with the Examiner that Sasaki *et al.* teach hybridizing a single stranded target polynucleotide with an abortive promoter cassette comprising a sequence that hybridizes to the single stranded target polynucleotide, and a region that can be detected by transcription by a polymerase. There is no such teaching in Sasaki *et al.* Sasaki *et al.* hybridize single stranded PCR primers (harboring T3 or T7 promoter sequence) to a single-stranded template and perform PCR to amplify a double-stranded template DNA having T3 or T7 promoter sequence contained therein.

Moreover, while both methods of Sasaki *et al.* and Dattagupta call for the generation of nucleic acid constructs comprising promoter sequences, the methods of Sasaki *et al.* and Dattagupta are directed to different purposes, *viz.*, transcriptional sequencing and amplifying and detecting nucleic acids. The parameters and various steps involved in sequencing nucleic acids and amplifying and detecting it are not necessarily the same, and persons skilled in the art are aware that protocols that are useful for one application are not necessarily useful for the other. For example, persons skilled in the art are aware that when the amount of template is small, it must first be amplified to generate sufficient amounts of template before it can be sequenced according to the method of Sasaki *et al.* Figure 4 of Sasaki *et al.* clearly show that the template for the transcriptional sequencing reaction first has to be prepared and *amplified*

before the transcriptional sequencing reaction can begin. It is also very clear, especially from Table 1 of Sasaki *et al.*, that the sensitivity of transcriptional sequencing is highly dependent on the amount of template. For example, according to Table 1 of Sasaki *et al.*, the accuracy of the transcriptional sequencing reaction declines considerably when the amount of plasmid template decreases to 10 ng. However, Applicant respectfully points out that 10 ng of plasmid template DNA corresponds to a *very large number* of copies of DNA and is also a significant quantity of DNA. Applicant points out that template DNA for sequencing applications is typically prepared by PCR amplification or by isolating large amounts of plasmid DNA harboring the sequence of interest to be sequenced from bacteria.

Contrary to the Examiner's assertions, the method described by Dattagupta is not suitable for sequencing reactions and consequently, persons skilled in the art would not consider combining the teachings of Sasaki *et al.* of a transcriptional sequencing method, on the one hand, with methods for amplifying and detecting a target, on the other hand, as discussed by Dattagupta. Thus, the cited art would not prompt the skilled artisan to incorporate terminators into the method of Dattagupta for the purpose of transcriptional sequencing.

Dattagupta were interested only in *amplifying* and *detecting* nucleic acids from samples with *high sensitivity*. See col. 1, lines 11-15 of Dattagupta. In the absence of any amplification steps, biological or environmental samples, for example, do not contain large enough amounts of target DNA to be useful for any sequencing reaction. Thus, the disclosure of Dattagupta would not lead the skilled artisan to conduct transcriptional sequencing reactions because the amount of any potential target in

samples of interest in Dattagupta is too minute to be effective for sequencing. Therefore, there would have been no reason to incorporate chain terminators in the method of Dattagupta for transcriptional sequencing embodiments. Incorporating chain terminators in the method of Dattagupta, as is done in sequencing reactions, would only have diluted any potential signal that Dattagupta hoped to detect, and it would not have been useful for efficient transcriptional sequencing.

The Examiner has not established why a person of skill in the art would have had a reason to perform transcriptional sequencing in view of the disclosure by Dattagupta, or how such a person would have been able to successfully perform sequencing reactions using the Dattagupta method. At a minimum, the target nucleic acid of Dattagupta would first have to be amplified to a significant extent in order to generate sufficient quantities of nucleic acid for a sequencing reaction. However, the Examiner has not indicated how the cited art would have suggested amplifying the target nucleic acid of Dattagupta for transcriptional sequencing. Sasaki *et al.* show that that template is amplified by PCR using primers that harbor T3 or T7 promoter sequences, followed by transcription of the PCR product by RNA polymerase. However, Applicant notes that the amplification scheme by Sasaki *et al.* is remarkably similar to the TAS (transcription amplification system) scheme discussed in the specification of Dattagupta. Dattagupta describe TAS as follows:

> As in PCR, TAS uses a pair of oligoprimers to hybridize with opposite ends of a desired target sequence. The primers are chosen such that the extension products, after either a single extension or multiple cycles as in PCR, comprise transcription promoter sites. In the presence of a suitable promoter specific polymerase and ribonucleoside triphosphates (rNTPs), the extension products are themselves further amplified by transcription.

Col. 2, lines 7-15. Importantly, Dattagupta disparage the TAS scheme, along with PCR and LCR (ligase chain reaction) for amplifying nucleic acids. See col. 3, line 58 through col. 4, line 2; col. 1, line 45, through col. 2, line 15. Therefore, one of skill in the art would not have been motivated to amplify the template using the TAS scheme, which is similar to the scheme described by Sasaki *et al.*, let alone perform a transcriptional sequencing reaction.

Therefore, it is clear that the cited art provides no reason to perform transcriptional sequencing according to the combined teachings of Dattagupta and Sasaki *et al.* and the Examiner has not established why a person skilled in the art would have been prompted to perform a transcriptional sequencing reaction in view of the teachings of Dattagupta and Sasaki *et al.*

Accordingly, for at least this reason, the Examiner has not established a *prima facie* case of obviousness and Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

In addition, Applicant respectfully points out that the skilled artisan would not, in fact, be prompted by the teachings in the cited art to perform a transcriptional sequencing reaction because it would be much more cumbersome and laborious and much less efficient than the transcriptional sequencing reaction described by Sasaki *et al.* As discussed above, amplification of target nucleic acid from samples of interest would be necessary to generate sufficient amounts of target nucleic acid for sequencing applications. The amplified product would then have to be melted to form a single-stranded polynucleotide (as required by the claims) and ligated to the hairpin construct of Dattagupta. Skilled artisans are well aware that a DNA ligation reaction is an inefficient

process. The general inefficiency of ligation would be compounded in this case by the tendency of the amplified nucleic acid to reanneal and form a double-stranded nucleic acid. The reannealing would be much more efficient and rapid than the ligation reaction and would hinder the efficiency of the ligation of a single-stranded nucleic acid and the hairpin complex of Dattagupta. It is likely that only a small amount of single-stranded template ligated to the hairpin structure would be generated and that this would not be a sufficient quantity for transcriptional sequencing. It would require relatively large and inconvenient amounts of target nucleic acid and the hairpin complex to generate an amount sufficient for a transcriptional sequencing reaction according to the Sasaki *et al.* method. Improving the ligation efficiency and/or generating sufficient amounts of template would at the least be cumbersome and laborious as compared to Sasaki *et al.* and would require more steps. Therefore, Applicant respectfully asserts that the cited art provides no reason that would prompt a skilled artisan to incorporate a terminator into the method of Dattagupta.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

***The Second 103 Rejection***

The Examiner rejected claims 71, 113, 114, 130, 133, 135, 138-140, and 142-148 under 35 U.S.C. § 103(a) as allegedly unpatentable over Dattagupta in view of Sasaki *et al.* and Kang *et al.* (U.S. Pat. No. 6,268,131). The Examiner applied Dattagupta and Sasaki *et al.* as above and further indicated that Dattagupta does not disclose that an immobilized probe is employed in the method. The Examiner asserted that Kang *et al.*

disclose a method of sequencing nucleic acid via use of RNA dependent RNA polymerases wherein the transcription of the template is initiated by a promoter sequence. The Examiner further contended that Kang *et al.* teaches an embodiment wherein the primer is immobilized on a solid surface. The Examiner further asserted that it would have been *prima facie* obvious to one of ordinary skill in the art to combine the teachings in the cited art for the purpose of detection/characterizing pathogens in a sample. The Examiner contended that the skilled artisan would have been motivated to combine the cited art to detect pathogens, such as RNA-based pathogens, and would have had a reasonable expectation of success.

As noted above, Applicant's claims do not encompass transcriptional sequencing. Applicant's claims are directed to methods of detecting DNA or RNA in test samples using an abortive, reiterative process. Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicant has amended the claims to more particularly point out and distinguish that the oligonucleotide transcripts are generated by an abortive, reiterative process. Neither Dattagupta, either alone or in combination with Sasaki *et al.* or Kang *et al.* disclose or suggest an abortive, reiterative process as claimed and the skilled artisan would have no reason to perform such a method in view of the cited art.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

***The Third 103 Rejection***

The Examiner rejected claims 131 and 132 under 35 U.S.C. § 103(a) as allegedly unpatentable over Dattagupta in view of Sasaki *et al.* and further in view of Loewy (U.S. Pat. No. 5,914,229). The Examiner applied Dattagupta and Sasaki *et al.* as above. The Examiner asserted that Loewy discloses a double-stranded nucleic acid promoter which binds RNA polymerase, employed in a method comprising, *inter alia*, combining a target nucleic acid with at least one oligonucleotide, wherein the oligonucleotide or oligonucleotides include a double-stranded promoter, a single stranded segment of nucleic acid complementary to a segment of the target nucleic acid, and a poly-T tail. The Examiner asserted that one of ordinary skill would have recognized that the double stranded promoter construct of Loewy would have produced the same predictable result as that of the hairpin structure of Dattagupta. Applicant respectfully traverses this rejection.

For the same reasons discussed above, Applicant respectfully asserts that the Examiner's rationale for incorporating chain terminators in the method of Dattagupta is not relevant, because the claims specify that transcription occurs by a reiterative, abortive process. Neither Dattagupta, either alone or in combination with Sasaki *et al.* or Loewy disclose or suggest an abortive, reiterative process as claimed and the skilled artisan would have no reason to perform such a method in view of the cited art.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

***Obviousness-type Double Patenting***

The Examiner provisionally rejected claims 55-71, 113, 114, 130-135, 138-140, and 142-148 on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 26, 27, 103, 112 and 136-139 of copending Appl. No. 10/488,971. The Examiner also rejected claims 55-71, 113, 114, 130-135, 138-140, and 142-148 as allegedly unpatentable on the ground of nonstatutory obviousness-type double patenting over claims 1-22, 32-34, and 44 of copending Appl. No. 10/976,240. The Examiner further rejected claims 55-71, 113, 114, 130-135, 138-140 and 142-148 as allegedly unpatentable on the ground of nonstatutory obviousness-type double patenting over claims 11-27 of copending Appl. No. 10/425,037. Applicant respectfully traverses these rejections.

Applicant respectfully requests that the Examiner reconsider and withdraw these rejections, or hold the present rejections in abeyance, pending the identification of otherwise allowable subject matter, at which time Applicant will consider filing any necessary terminal disclaimers.

## *Conclusion*

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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